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Award Number: DAMD17-98-1-8294

TITLE: Isolation of Genes from Chromosome Region Ip31 Involved in the Development of Breast Cancer

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REPORT DATE: September 2001

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	September 2001	Annual (1 Sep 00 - 31 Aug 01)

4. TITLE AND SUBTITLE
Isolation of Genes from Chromosome Region Ip31 Involved in the Development of Breast Cancer

5. FUNDING NUMBERS
DAMD17-98-1-8294

6. AUTHOR(S)
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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE

13. Abstract ***(Maximum 200 Words)*** *(abstract should contain no proprietary or confidential information)*

The p31 region of chromosome 1 shows frequent (50%) loss of heterozygosity (LOH) in breast tumors. This observation implies the presence of a tumor suppressor gene in this region which, when mutated contributes to tumorigenesis. The maximal common region undergoing LOH extends over approximately 2Mbp. We have constructed a map of overlapping BAC clones spanning this region with only 4 gaps. The total available sequence from this region suggests that approximately 50-60% of it is now completed. Using gene analysis tools, we have been able to demonstrate that few full-length genes are located in this region and that the ESTs from the databases are clustered to a proximal position of the contig. The high level of sequencing completed from this region means that it will soon be possible to establish a baseline transcription map. The genes identified in this way can now be tested systematically for mutations in breast tumors. The progesterone receptor gene lies at the limit of the region suggesting that it was possibly the target for LOH. We established the exon/intron structure of this gene and undertook SSCP analysis of breast tumors. No gene-inactivating mutations were found excluding this gene from involvement in breast cancer development.

14. SUBJECT TERMS	15. NUMBER OF PAGES
Breast Cancer	5
	16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

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INTRODUCTION:

Loss of hetereozygosity (LOH) is a mechanism which has been identified in virtually all tumor types analyzed. The molecular assay reveals areas of the genome which have lost one copy of a particular region of a chromosome. It is considered a method by which tumor cells lose the copy of a normal gene but retain a defective copy thus exposing a recessive mutation in a critical gene. LOH analysis of breast cancer has shown that over 50% of tumors lose genetic material from the short arm of chromosome 1, centered on the 1p31 region. We have previously defined a 1.5 Mbp region in 1p31 which is consistently lost in the majority of reported cases where this region was investigated. With the sequencing of the human genome and the availability of genetic annotations of this region which describe the genes located there we have been undertaking a mutation screen in breast tumors of candidate genes. We have excluded the TTC4 gene and the progesterone receptor gene both of which were excellent candidates since they were expressed in normal breast tissue and located within the frequently deleted region. These experiments were completed in the second year and the subject of previous reports.

BODY:

In October 2000 the P.I. accepted the position of Chair of Cancer Genetics at Roswell Park Cancer Institute and moved his laboratory there in November 2000. The USAMRMC was informed of this change of institution at that time and the paperwork to transfer the grant funding was submitted at the beginning of 2001. As of the 30th of September 2001 this transfer has still not taken place and no assurances that it will be completed could be obtained. As a consequence we have been unable to pursue any of the experimental objectives outlined in the statement of work for the final year of this grant. The outstanding tasks therefore remain as they did at the end of the second year.

Task 1:	Completed
Task 2:	Completed
Task 3:	Deleted - with the progress of the genome sequencing project this task became redundant.
Task 4:	Completed
Task 5:	Completed
Task 6:	In progress
Task 7:	Deleted - with the progress of the genome sequencing project this task became redundant.

The search for the critical 1p31 gene is now relatively straightforward since there are a number of candidate genes in the region which have been identified as a result of the generation of the human genome sequence. We have searched the Public databases and the Celera database to identify genes as well as define their exon/intron structure. We are now poised to undertake mutation analyses as described in the original application which is dependent on the transfer of the remaining funding for the project to hire personnel who will be dedicated to this task.

KEY RESEARCH ACCOMPLISHMENTS:
No progress due to the non-transfer of funding to the new Institution.

REPORTABLE OUTCOMES:
No progress due to the non-transfer of funding to the new Institution.

CONCLUSIONS:
No progress due to the non-transfer of funding to the new Institution

REFERENCES:
None

APPENDICES:
None